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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/574,460	05/18/2000	Michael A. Apicella	17023.004US1	6817

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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/574,460	APICELLA ET AL.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/10/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The final amendment filed on October 10, 2005, amending claims 30, 35-37, 39, 44-46, 48 and 52-54, has been entered.

Claims 30-55 are pending and are under consideration.

The finality of the rejection of the last Office action is withdrawn.

Response to Arguments

Applicant's amendment and arguments filed on October 10, 2005, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 30 and claims 31-38 depending therefrom rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 recites the phrase "*Haemophilus influenzae*-specific lipooligosaccharide (LOS)". The metes and bounds of the phrase in the context of the above claim are not clear to the Examiner. It is not clear to the Examiner what is considered as "*Haemophilus influenzae*-specific" by the applicants. A perusal of the specification did

not provide a clear definition for the above phrase. Without a clear definition, those skilled in the art would be unable to conclude if a LOS is indeed a "*Haemophilus influenzae*-specific" LOS without knowing the metes and bounds of the phrase.

Claim 48 and claims 49-55 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 48 recites the phrase "modifying a terminal heptose of a lipopolysaccharide (LPS) or lipooligosaccharide (LOS) core structure". The metes and bounds of the phrase in the context of the above claim are not clear to the Examiner. It is not clear to the Examiner whether adding an N-acetyl glucosamine to the terminal heptose is "modifying" the heptose or if other "modifications" are encompassed by the above phrase. Examiner requests clarification of the above phrase.

Claims 36, 45 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 36, 45 and 53 recite the phrase "*rfe* is part of the gram-negative bacterial genome". The metes and bounds of the phrase in the context of the above claim are not clear to the Examiner. It is not clear to the Examiner either from the specification or from the claims as what applicants mean by the term "part". It is also not clear to the Examiner whether "rfe" is endogenous to the genome of the gram-negative bacteria

recited in line of claim 30 or if "rfe" has been transformed into the genome of the gram-negative bacteria. Examiner requests clarification of the above phrase.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 30-55 are drawn to a method of producing a *H. influenzae* specific lipooligosaccharide (LOS) or complex carbohydrate by culturing a gram-negative bacteria comprising a polynucleotide encoding an Undecaprenyl-phosphate N-acetyl glucosaminyl phosphate transferase (rfe), wherein said bacteria is transformed with a polynucleotide encoding a lipooligosaccharide-synthesis gene G polypeptide (lsgG) from *H. influenzae*, wherein a terminal heptose of a lipopolysaccharide (LPS) or LOS core structure of said gram-negative bacterial species is modified by the addition of N-acetyl glucosamine. The claims encompass a method of producing any or all *H. influenzae* specific LOS or any or all complex carbohydrates by altering the terminal heptose of any LPS or LOS core structure by transforming any or all Gram-negative bacteria, *E. coli* or *S. minnesota* with any or all polynucleotides encoding a LsgG from

H. influenzae, including any or all variants, mutants and recombinants thereof, wherein said Gram-negative bacteria, *E. coli* or *S. minnesota* endogenously comprises any or all polynucleotides encoding a rfe from any source or are transformed with any or all polynucleotides encoding a rfe from *H. influenzae*, including any or all variants, mutants and recombinants thereof. Therefore, the claims are drawn to a method of producing (A) a genus comprising any or all *H. influenzae* specific LOS or any or all complex carbohydrates having any structure by altering the terminal heptose of any or all LPS or LOS core structure having any structure in (B) a genus comprising any or all Gram-negative bacteria, *E. coli* or *S. minnesota*, wherein said bacteria is transformed with (C) a genus comprising any or all polynucleotides encoding a LsgG from *H. influenzae,* having any structure and (D) is transformed with a genus of any or all polynucleotides encoding a rfe from any source or *H. influenzae* having any structure if said bacteria endogenously does not produce rfe.

The specification only describes a method of producing specific LOS described in Table 2 and 3 by transforming *E. coli* with a polynucleotide encoding lsgG isolated from *H. influenzae* (pGEMLOS-4, pGEMLOS-5 or PGEMLOS-7), wherein the polynucleotide encoding rfe is endogenous to the *E. coli.* This one example is not enough and does not constitute a representative number of species to describe the whole genus comprising any or all LOS, genus comprising any or all Gram-negative bacteria, genus comprising any or all polynucleotides encoding rfe or genus comprising any or all polynucleotides encoding lsgG. There is no evidence on the record of the relationship between the structure of the polynucleotide encoding lsgG in pGEMLOS-4 and the

structure of any or all polynucleotides encoding lsgG, including any or all recombinants, mutants and variants thereof. Similarly, there is no evidence on the record of the relationship between the structure of the polynucleotide encoding rfe endogenous to E. coli and the structure of any or all polynucleotide encoding rfe, including any or all recombinants, mutants and variants thereof. There is also no evidence on the record of a method for successfully producing any or all LOS in any or all Gram-negative bacteria. Therefore, the specification fails to describe a representative species of the genus comprising any or all polynucleotides encoding rfe and genus comprising any or all polynucleotides encoding lsgG and used to transform a genus comprising any or all Gram-negative bacteria to produce any or all H. influenzae specific LOS.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 30-55.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 30-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing specific LOS described in Table 2 and 3 by transforming *E. coli* with a polynucleotide encoding lsgG isolated from

H. influenzae (pGEMLOS-4, pGEMLOS-5 or PGEMLOS-7), wherein the polynucleotide encoding rfe is endogenous to the *E. coli*, does not reasonably provide enablement for a method of producing (A) any or all *H. influenzae* specific LOS or any or all complex carbohydrates having any structure by altering the terminal heptose of any or all LPS or LOS core structure having any structure by transforming (B) a genus comprising any or all Gram-negative bacteria, *E. coli* or *S. minnesota* with (C) a genus of any or all polynucleotides encoding a rfe from any source or *H. influenzae* having any structure and (D) a genus comprising any or all polynucleotides encoding a LsgG from *H. influenzae,* having any structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 30-55 are drawn to a method of producing a H. influenzae specific lipooligosaccharide (LOS) or complex carbohydrate by culturing a gram-negative bacteria comprising a polynucleotide encoding an Undecaprenyl-phosphate N-acetyl glucosaminyl phosphate transferase (rfe), wherein said bacteria is transformed with a

polynucleotide encoding a lipooligosaccharide-synthesis gene G polypeptide (lsgG) from Haemophilus influenzae, wherein the terminal heptose of a lipopolysaccharide or LOS core structure of said gram-negative bacterial species is modified by the addition of N-acetyl glucosamine. The claims encompass a method of producing any or all *H. influenzae* specific LOS or any or all complex carbohydrates by altering the terminal heptose of any LPS or LOS core structure by transforming comprising any or all Gram-negative bacteria, *E. coli* or *S. minnesota* comprising any or all polynucleotides encoding a rfe from any source or *H. influenzae*, including any or all variants, mutants and recombinants thereof, with any or all polynucleotides encoding a LsgG from *H. influenzae,* including any or all variants, mutants and recombinants thereof. Therefore, the claims are drawn to a method of producing (A) any or all *H. influenzae* specific LOS or any or all complex carbohydrates having any structure by altering the terminal heptose of any or all LPS or LOS core structure having any structure in (B) any or all Gram-negative bacteria, *E. coli* or *S. minnesota*, wherein said bacteria is transformed with (C) any or all polynucleotides encoding a LsgG from *H. influenzae,* having any structure and (D) is transformed with any or all polynucleotides encoding a rfe from any source or *H. influenzae* having any structure if said bacteria endogenously does not produce rfe.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the use of extremely large number of polynucleotides encoding lsgG and rfe, including variants, mutants and recombinants thereof, used to transform any gram-negative bacterial to produce any or all H. influenzae specific LOS,

broadly encompassed by the claims. Since the amino acid sequence of the encoded protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a method of producing specific LOS described in Table 2 and 3 by transforming *E. coli* with a polynucleotide encoding lsgG isolated from *H. influenzae* (pGEMLOS-4, pGEMLOS-5 or PGEMLOS-7), wherein the polynucleotide encoding rfe is endogenous to the *E. coli*. It would require undue experimentation of the skilled artisan to make and use the claimed polynucleotides encoding variants and mutants of any rfe or lsgG, wherein any Gram –negative bacteria transformed with said polynucleotides produces *H. influenzae* specific LOS. In view of the great breadth of the claim, amount of experimentation required to make the claimed polynucleotides and LOS, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polynucleotides and host cells encompassed by the method of these claims to produce *H. influenzae* specific LOS .

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple

modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass a method of producing (1) any or all *H. influenzae* specific LOS or any or all complex carbohydrates having any structure by altering the terminal heptose of any or all LPS or LOS core structure having any structure by transforming (2) any or all Gram-negative bacteria, *E. coli* or *S. minnesota* with (3) any or all polynucleotides encoding a rfe from any source or *H. influenzae* having any structure and (4) any or all polynucleotides encoding a LsgG from *H. influenzae,* having any structure, because the specification does not establish: (A) regions of the encoded proteins whose structure which may be modified without affecting its activity of synthesizing *H. influenzae* specific LOS in gram-negative bacteria normally producing only LPS ; (B) the general tolerance of said proteins to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue on these proteins with an expectation of obtaining the desired biological function; (D) a universal method of producing *H. influenzae* specific LOS in gram-negative bacteria normally producing only LPS; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including the use of any or all polynucleotides encoding rfe or lsgG in any gram-negative bacteria to produce *H. influenzae* specific LOS. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any or all any or all polynucleotides encoding rfe or lsgG, including variants, mutants and recombinants thereof, having the desired biological characteristics recited in the claim and production of *H. influenzae* specific LOS in any gram-negative bacteria transformed with said polynucleotides is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless –**
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30-34, 36-41, 43, 45-50, and 53-55 are rejected under 35 U.S.C. 102(b) as being anticipated by McLaughlin et al.

Claims 30-34, 36-41, 43, 45-50, and 53-55 are drawn to a method of producing LOS or complex carbohydrate and a method of adding a N-acetyl glucosamine to a terminal heptose of a LOS or LPS core structure using an *E. coli* K-12 strain JM109, transformed with a polynucleotide encoding a lsgG from *H. influenzae*, wherein a polynucleotide encoding rfe is part of said *E. coli's* genome and said rfe is regulated by said LsgG.

McLaughlin et al. (form PTO-1449) discloses to a method of producing *H. influenzae* specific LOS, a complex carbohydrate, using an *E. coli* K-12 strain JM109 transformed with a polynucleotide encoding a lsgG from *H. influenzae*, wherein said *E. coli* endogenously comprises a polynucleotide encoding a rfe polynucleotide (pages 165-166). The LOS produced is *H. influenzae* specific since it is recognized by antibodies raised against *H. influenzae* LOS (pages 166, 170 and 172). In the method of McLaughlin et al., N-acetyl glucosamine is added to a terminal heptose of a LOS or LPS core structure. The *E.coli* of McLaughlin et al. inherently possesses a polynucleotide encoding rfe since *E. coli* endogenously produces rfe (See Alexander et al. – form PTO-1449) and the claims do not recite transforming *E. coli* with rfe. Regulation of rfe by LsgG is an inherent property of LsgG, which would flow naturally when both polynucleotides are present. Therefore, the reference of McLaughlin et al. anticipates claims 30-34, 36-41, 43, 45-50, and 53-55

Since the Office does not have facilities for examining and comparing applicant's *E. coli* and the *E. coli* of McLaughlin et al. used in the method of McLaughlin et al.., the burden is on the applicant to show a novel or unobvious difference between the product

used in the claimed method and the product used in the prior art (i.e., that the *E. coli* transformant of the prior art does not possess the same material structure and functional characteristics of the claimed *E. coli* transformant). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Figzgerald* et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33, 35, 42, 44 and 51-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over *McLaughlin* et al. in view of Preston et al. and Swierzko et al.

Claims 33, 35, 42, 44 and 51-52 are drawn to a method of producing LOS or complex carbohydrate and a method of adding a N-acetyl glucosamine to a terminal heptose of a LOS or LPS core structure using a *S. minnesota* transformed with a polynucleotide encoding a rfe from *H. influenzae* and a polynucleotide encoding a LsgG from *H. influenzae*.

McLaughlin et al. discloses to a method of producing LOS or complex carbohydrate using an *E. coli* K-12 strain JM109 which comprises a polynucleotide encoding a rfe and wherein said *E. coli* is transformed with a polynucleotide encoding a LsgG from *H. influenzae*, as discussed above.

The reference of McLaughlin et al. does not teach a method of transforming a S. minnesota with a polynucleotide encoding a rfe from *H. influenzae.*

Preston et al. (form PTO-1449) discloses several genes involved in LOS biosynthesis, including the lsg gene and rfe gene isolated from *H. influenzae* (Table page 154). Preston et al. teaches that *H. influenzae* produce LOS lacking O-antigens, which are present in LPS produced by most Gram-negative bacteria. Alexander et al. (from PTO-1449) confirms said teaching by disclosing that the rfe gene isolated from *E. coli* is involved in O-antigen synthesis of LPS (page 7079, abstract).

Swierzko et al. (cited previously on form PTO-892) discloses that *S. minnesota* bears a terminal heptose molecule and discloses using this bacterium as a transformant in synthesizing LPS (pages 3216-3217). *S. minnesota* is an useful host due to their rapid growth in the laboratory (page 3216) and produces LPS.

Therefore, in combining the teachings of Phillips et al., McLaughlin et al. and Swierzko et al, it would have been obvious to one having ordinary skill in the art modify the method of McLaughlin et al. by transforming *E. coli* or *S. minnesota* et al. with the rfe gene of Preseton et al. in addition to the lsg gene. One of ordinary skill in the art would have been motivated to use the rfe gene of Preston et al. in gram-negative bacterium producing LPS with O-antigens, such as *E. coli* and *S. minnesota*, in order to produce *H. influenzae* specific LOS, which lack O-antigens in their structure. One of ordinary skill in the art would have had a reasonable expectation of success since Preston et al. teaches a rfe gene and Swierzko et al. teaches using *S. minnesota* as a effective transformant.

Therefore, the above references render claims 33, 35, 42, 44 and 51-52 *prima facie* obvious to one of ordinary skill in the art.

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652

Manjunath Rao
Primary Patent Examiner 1652